H5N1 viral-engineering dangers will not go away

Governments, funders and regulatory authorities must urgently address the risks posed by gain-of-function research, says **Simon Wain-Hobson**.

Barely two months after a small group of influenza virologists lifted a moratorium on work to make the H5N1 avian flu virus as transmissible between humans as seasonal flu, researchers are at it again. Earlier this month, a Dutch scientist proposed similar experiments with other avian flu viruses, as well as the SARS coronavirus. And a fortnight ago, scientists in Germany and Switzerland reported how they had tweaked canine distemper virus to make it grow in human cells.

The logic behind these kinds of experiments, collectively called gain-of-function (GOF) research, is to identify combinations of mutations that could allow an animal virus to jump to unprepared humans. By knowing the mutations, the thinking goes, we can better prepare and marshal our scientific defences against a possible threat.

GOF research on avian flu provoked heated controversy, much of it covered by this journal. That controversy did not go away with the lifting of the moratorium. On the contrary, it continues to fester. Officials in Washington DC are putting the finishing touches to new guidelines for the review, regulation and oversight of this kind of research. The chill winds that we can anticipate blowing from policy-makers as a result could affect all of us who research viruses and their pathology. To avoid this, researchers in this field need to learn lessons from the past.

Rather than use the avian flu moratorium to seek advice, listen and foster debate, many influenza scientists engaged in an academic exercise of self-justification. There was a single large open meeting, at the Royal Society in London, which engaged a wider audience, including bioethicists. The recent calling off of the moratorium by 40 flu researchers alone — not funders, governments or international bodies — says it all. The flu community simply hasn't understood that this is a hot-button issue that will not go away.

There are parallels here to my own field of HIV. In the early days of research, HIV scientists, buoyed by huge research monies, exuded hubris, promised a vaccine within two years, and all sorts of other things. The crunch came when they realized they had to engage seriously with patient groups. The result is that HIV patients became the most faithful collaborators of HIV clinicians. It is too easy for scientists in a field to dismiss criticism and ideas from outside.

Here are the issues that must be openly addressed about gain-of-function work with avian flu, the SARS coronavirus — or any other virus.

First, is the virological basis for the work sound? The outcomes of the H5N1 experiments are dominated by the artificial-selection systems used. If aerosol-transmitted virus is systematically passaged from ferrets with severe respiratory distress, then the research teams will end up with a transmissible and highly virulent strain. Likewise, if animals with mild symptoms are chosen, a transmissible virus of low virulence would ultimately emerge. Whether nature will take any of these courses is unknown. Take dog breeding. Ruthless selection of alleles over a short period has produced phenomenal phenotypic variation — dachshunds, salukis, whippets and setters. Would nature have come up with the dachshund?

Second, infectious-disease researchers are fond of saying that microbes do not respect barriers. So who makes the rules and provides oversight? Barely a sound has emerged at international level. The World Health Organization has held essentially closed-door meetings and has failed singularly to widen the debate.

Third, what if these groups generate a highly pathogenic and transmissible virus — which I suspect, within two years, they will? Then what? Should the virus be shared? Should research be highly restricted to this novel virus strain of catastrophic potential?

Fourth, what if there was a leak or a small outbreak? Crippling lawsuits would follow. Are the academic institutions sufficiently covered in terms of insurance? Are university regents or chancellors even aware of the power, and dangers, of the modern molecular biology going on in their labs? Again, not a word has emerged.

Fifth, the world has never been more densely populated. Is it appropriate for civilian scientists to make microbes more dangerous? Is creating a novel human virus antisocial? Was there a failure of duty on behalf of funders and regulators? What is the ethical position on such work? Here there has been a start, but as yet there is no consensus.

The global ramifications of GOF research have simply not been sufficiently explored and discussed. Influenza virologists are going down a blind alley and the powers that be are blindly letting them travel unaccompanied, which is tantamount to acquiescing. So let's be clear: the end game could be viruses more dangerous than the Spanish flu strain.

H5N1 GOF work — indeed all virological GOF work — should be suspended until virologists open up and engage in public discussion of their work and the issues it raises. Given that the flu community failed utterly to use the year-long hiatus to good effect, it is clear that an independent risk–benefit assessment of GOF work is needed.

Governments, funders and regulatory authorities should encourage the influenza virologists to listen and discuss. Learned societies should get off the fence and speak out. A conference involving all the stakeholders is needed, as happened at Asilomar in the 1970s for recombinant DNA. The problem will not go away. It has to be engaged and it has to be done now. ■

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